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Abstract: **BACKGROUND:** Hypofibrinogenaemia is one of the main reasons for development of peri-operative coagulopathy during major paediatric surgery. The aim of this study was to assess whether prophylactic maintenance of higher fibrinogen concentrations through administration of fibrinogen concentrate would decrease the volume of transfused red blood cell (RBCs). **METHODS:** In this prospective, randomised, clinical trial, patients aged 6 months to 17 yr undergoing craniostomosis and scoliosis surgery received fibrinogen concentrate (30 mg kg⁻¹) at two predefined intraoperative fibrinogen concentrations [ROTEM(®) FIBTEM maximum clot firmness (MCF) of <8 mm (conventional) or <13 mm (early substitution)]. Total volume of transfused RBCs was recorded over 24 h after start of surgery. **RESULTS:** Thirty children who underwent craniostomosis surgery and 19 children who underwent scoliosis surgery were treated per protocol. During craniostomosis surgery, children in the early substitution group received significantly less RBCs (median, 28 ml kg⁻¹; IQR, 21 to 50 ml kg⁻¹) compared with the conventional fibrinogen trigger of <8 mm (median, 56 ml kg⁻¹; IQR, 28 to 62 ml kg⁻¹) (P=0.03). Calculated blood loss as per cent of estimated total blood volume decreased from a median of 160% (IQR, 110-190%) to a median of 90% (IQR, 78-110%) (P=0.017). No significant changes were observed in the scoliosis surgery population. No bleeding events requiring surgical intervention, postoperative transfusions of RBCs, or treatment-related adverse events were observed. **CONCLUSIONS:** Intraoperative administration of fibrinogen concentrate using a FIBTEM MCF trigger level of <13 mm can be successfully used to significantly decrease bleeding, and transfusion requirements in the setting of craniostomosis surgery, but not scoliosis. **CLINICAL TRIAL REGISTRY NUMBER:** ClinicalTrials.gov NCT01487837.

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CLINICAL PRACTICE

Higher fibrinogen concentrations for reduction of transfusion requirements during major paediatric surgery: A prospective randomised controlled trial[†]

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Abstract

Background: Hypofibrinogenaemia is one of the main reasons for development of perioperative coagulopathy during major paediatric surgery. The aim of this study was to assess whether prophylactic maintenance of higher fibrinogen concentrations through administration of fibrinogen concentrate would decrease the volume of transfused red blood cell (RBCs).

Methods: In this prospective, randomised, clinical trial, patients aged 6 months to 17 yr undergoing craniostomy and scoliosis surgery received fibrinogen concentrate (30 mg kg⁻¹) at two predefined intraoperative fibrinogen concentrations [ROTEM[®] FIBTEM maximum clot firmness (MCF) of <8 mm (conventional) or <13 mm (early substitution)]. Total volume of transfused RBCs was recorded over 24 h after start of surgery.

Results: Thirty children who underwent craniostomy surgery and 19 children who underwent scoliosis surgery were treated per protocol. During craniostomy surgery, children in the early substitution group received significantly less RBCs (median, 28 ml kg⁻¹; IQR, 21 to 50 ml kg⁻¹) compared with the conventional fibrinogen trigger of <8 mm (median, 56 ml kg⁻¹; IQR, 28 to 62 ml kg⁻¹) ($P=0.03$). Calculated blood loss as per cent of estimated total blood volume decreased from a median of 160% (IQR, 110–190%) to a median of 90% (IQR, 78–110%) ($P=0.017$). No significant changes were observed in the scoliosis surgery population. No bleeding events requiring surgical intervention, postoperative transfusions of RBCs, or treatment-related adverse events were observed.

Conclusions: Intraoperative administration of fibrinogen concentrate using a FIBTEM MCF trigger level of <13 mm can be successfully used to significantly decrease bleeding, and transfusion requirements in the setting of craniostomy surgery, but not scoliosis.

Clinical trial registry number: ClinicalTrials.gov NCT01487837.

Key words: blood, coagulation; coagulation; coagulopathy; hemorrhage; pediatrics; thrombelastography; transfusion

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Editor's key points

- Hypofibrinogenaemia can lead to acquired coagulopathy after major paediatric surgery.
- The effect of a liberal fibrinogen concentrate treatment strategy on red blood cell transfusion was studied in a single centre randomised study of craniosynostosis and scoliosis surgery patients.
- Thromboelastometry-guided maintenance of high normal fibrinogen concentrations reduced blood loss and transfusion in craniosynostosis surgery.

Major paediatric surgery is frequently associated with extensive blood loss, which increases the risk for morbidity and mortality.¹ The risks associated with transfusion highlight the urgent need for blood conserving strategies, especially in children. These include implementation of patient blood management programs with coagulation management.^{2–3} Both major paediatric orthopaedic surgery and craniosynostosis surgery are frequently associated with moderate to severe bleeding.^{4–6} The development of hypofibrinogenaemia is a major reason for coagulopathic bleeding during craniosynostosis surgery.⁷ A prospective observational trial in adolescents who underwent major spine surgery demonstrated that preoperative fibrinogen concentrations predict mean total perioperative blood loss.⁴ Thus, restoration of adequate fibrinogen concentrations plays a major role in maintenance of effective haemostasis.

As in most European countries cryoprecipitate is not available, and fresh frozen plasma (FFP) has demonstrated questionable efficacy in restoring diminished fibrinogen concentrations after perioperative bleeding,^{8–10} administration of purified fibrinogen concentrate has become the standard of care in a number of countries, including Switzerland. Fibrinogen concentrate is recommended in the current European guidelines for perioperative bleeding management,¹¹ although data in children are rare.^{7,12} In the previously mentioned studies, targeted fibrinogen administration was successfully implemented using the ROTEM® FIB-TEM assay (TEM International, Munich, Germany) to monitor and guide fibrinogen substitution, applying a trigger level of FIB-TEM MCF <8 mm.¹¹

The aim of this study was to assess if earlier substitution of fibrinogen without waiting for hypofibrinogenaemia, defined as FIBTEM MCF <8 mm, decreases blood loss and consequently transfusion of allogeneic blood products. We hypothesized that maintenance of baseline fibrinogen concentrations for this population¹³ (ROTEM® trigger of FIBTEM MCF <13 mm) can reduce the need for transfusion of red blood cells (RBC's) in two types of major paediatric surgery.

Methods**Study design and population**

This phase IV, prospective, randomised, single-blinded, parallel-group, stratified clinical trial was conducted at a single children's hospital (University Children's Hospital, Zurich, Switzerland). The study was approved by the local ethics committee (KEK-ZH-No. 2011-0440) and the Swiss Regulatory Medical Authorities (registration No.: 2011 DR 4222), conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and registered at ClinicalTrials.gov identifier No. NCT01487837.

Eligible male and female patients between 6 months and 17 yr of age who were to have elective craniosynostosis or scoliosis

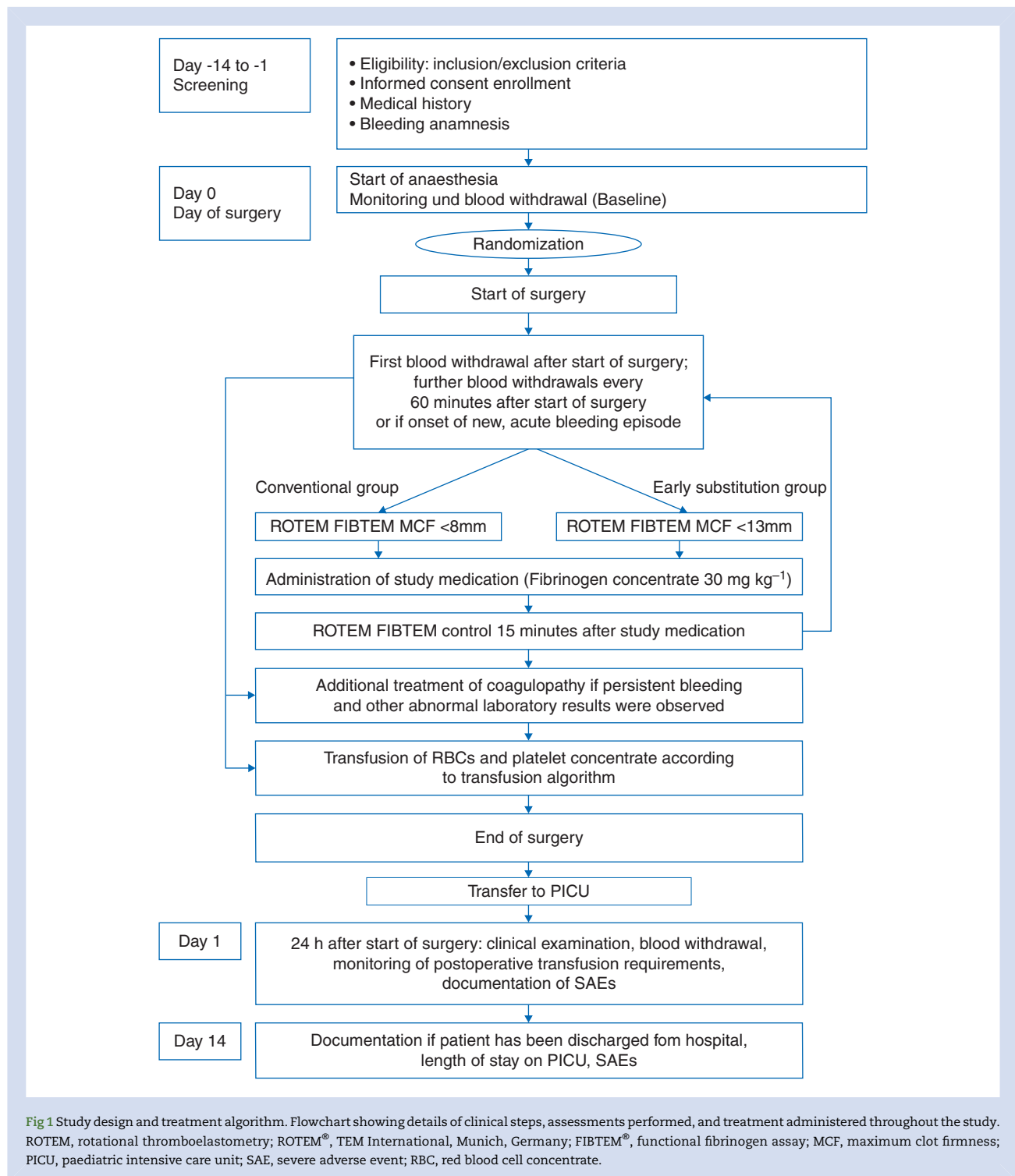
surgery were enrolled between February 2012 and September 2014, if informed consent of one parent was obtained. Craniosynostosis surgery was defined as anterior vault reconstruction with fronto-orbital advancement, and scoliosis surgery as dorsal instrumentation of more than 6 segments. Exclusion criteria encompassed any diagnosed preexisting congenital or acquired coagulation disorder, a medical history consistent with increased bleeding tendency, ongoing anticoagulation therapy or drug intake that could cause bleeding, clinical signs or diagnosis of acute thromboembolism, participation in another clinical trial, and pregnant or lactating women.

A telephone randomisation system was used. Before starting the trial, a randomisation list, stratified by procedure, was prepared by a statistician and sent to dedicated, trained staff members in our hospital pharmacy. After the start of anaesthesia for a consented study patient, the investigator retrieved the randomisation group by calling the pharmacy. Patients were randomised to one of the treatment groups after the start of anaesthesia and stratified by type of surgery (craniosynostosis or scoliosis surgery).

Procedures

All subjects in this study received antifibrinolytic prophylaxis by administration of tranexamic acid (TXA) at an initial dose of 15 mg kg⁻¹ followed by continuous infusion of 1.5 mg kg⁻¹ h⁻¹ until 3 h after transfer to the paediatric intensive care unit (PICU). Laboratory investigation (cell count, blood gas analysis, standard plasmatic coagulation testing, factor XIII, and ROTEM® analysis) was performed after induction of anaesthesia, at the start of surgery, and every 60 min thereafter, or more frequently at the discretion of the anaesthetist in charge, if acute bleeding was present (Fig. 1). Laboratory testing, including ROTEM® analyses, was performed at the hospital's central laboratory with real-time online access to ROTEM® traces from the operating theatre. ROTEM® FIBTEM MCF could usually be obtained within 15 min of blood draw. Fibrinogen concentrate was administered for ROTEM® FIBTEM MCF <8 mm (conventional group) or <13 mm (early substitution group), at any intraoperative measurement, independent of the presence of bleeding. The trigger of <8 mm in the conventional group was established based on the recommendation from a European guideline,¹¹ and the concentration of <13 mm represents the baseline fibrinogen concentrations for this population.¹³ Fibrinogen concentrate (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was administered at a dose of 30 mg kg⁻¹ if indicated according to the predefined FIBTEM concentrations by pump-controlled i.v. administration over 10 min. This dose and the indication of acquired hypofibrinogenaemia is within the labelling for this drug in Switzerland, and likewise published in a European guideline for perioperative bleeding management in children.¹¹ FIBTEM was also performed 10 min after the end of fibrinogen administration and fibrinogen concentrate was repeatedly administered if threshold FIBTEM concentrations were not reached.

Body temperature was continuously monitored and all children were kept normothermic during the procedure to ensure physiologic conditions for haemostasis. Red blood cell concentrates (RBCs) were transfused following a strict transfusion protocol for haemoglobin concentrations <8 g dl⁻¹ with a 10 g dl⁻¹ haemoglobin concentration target. Transfused RBC volume was calculated by approximating that transfusion of 4 ml kg⁻¹ RBC increases haemoglobin by 1 g dl⁻¹.¹⁴ If intraoperative blood salvage with a mechanically processed autologous transfusion (MAT) device was performed, the autologous blood concentrate was used



as a replacement for RBCs, using the same dose calculation. Apheresis platelets were transfused at a dose of 20 ml kg^{-1} for platelet count $<50\,000 \mu\text{l}^{-1}$. The concomitant coagulation management algorithm consisted of administration of factor XIII concentrate (Fibrogammin, CSL Behring GmbH, Marburg, Germany), at a dose of 20 IU kg^{-1} for intraoperative factor XIII concentrations $<30\%$, or between $30\text{--}60\%$ during an episode of ongoing bleeding requiring transfusion.

Basic fluid management consisted of infusing Ringer's acetate solution with 1% glucose (Bichsel AG, Interlaken, Switzerland) and/or Ringer's acetate solution (Fresenius Kabi, Oberdorf, Switzerland), at hourly rates of $10\text{--}20 \text{ ml kg}^{-1} \text{ h}^{-1}$, while a 4% succinylated gelatin solution (Physiogel balanced, B Braun AG, Sempach, Switzerland) or 5% albumin solution (CSL Behring, Bern, Switzerland) was administered additionally to compensate for estimated blood loss.

After transfer to the PICU, the applied transfusion algorithm consisted of transfusion of 20 ml kg⁻¹ RBCs for haemoglobin concentration <7 g dl⁻¹, 20 ml kg⁻¹ for platelets if platelet count <50 000 µl⁻¹, or transfusion of 20 ml kg⁻¹ FFP for significant bleeding. This represents the current standard of care in our PICU. Patients were extubated (if not previously performed intraoperatively) and transferred to the general ward at the discretion of the intensivist in charge. The staff in the PICU were blinded to the randomisation group. Twenty-four hours after the start of surgery a final blood withdrawal was performed and the occurrence of re-bleeding, postoperative transfusion or coagulation therapy, or severe adverse events (SAEs) were monitored and documented. SAEs were defined as any deterioration of patient status that led to death or occurrence of a life threatening situation, major disability, prolonged hospitalisation, or any other clinically relevant change in a patient status. Events were rated as treatment-emergent if any signs of thromboembolic events were observed. At day 14 after surgery, medical charts were reviewed to assess discharge status, SAEs, episodes of re-bleeding, or need for revision surgery in the postoperative period.

Study endpoints

The primary endpoint was the total volume of transfused RBCs per kg bodyweight (including transfused salvaged autologous blood) within 24 h after start of surgery. Secondary endpoints included requirements for all other transfused blood products, intraoperative blood loss based on the estimated total blood volume (calculated as described by Kearney¹⁵), length of stay in the PICU, discharge status at day 14 after surgery, and occurrence of bleeding that required revision surgery. Treatment-related adverse events that occurred within 14 days after surgery were assessed and recorded. In accordance with Good Clinical Practice, the study principal investigator evaluated safety data throughout the study.

Statistical analysis

Sample size calculation for stratified procedures was based on data from our institution, showing a standard deviation of 0.31 of the log10-transformed volume (mL) of transfused RBCs. A clinically meaningful reduction for RBC transfusion was defined as 50% (i.e. 0.3 on the log-scale). A power of 80% and a two-sided type I error of 0.05 revealed a number of 18 patients per group using unpaired t-test. For a better estimation of clinical relevance, 30 patients were scheduled for each group.

Continuous data are presented as mean (SD) or median (IQR), and are compared between groups using the Mann-Whitney U-test. Categorical data are presented as number with percentage and are compared between groups using the χ^2 test or Fisher's exact test where appropriate. The effect of maintenance of normal fibrinogen concentrations on volume of transfused RBCs was assessed using multiple linear regression, with square root transformed volume of transfused RBCs as the dependent variable, and maintenance of fibrinogen concentrations at ≥ 13 mm FIBTEM MCF and type of surgery as independent variables. Validity of the linear regression was assessed graphically using Q-Q- and Tukey-Anscombe plots. Two-sided $P < 0.05$ were considered statistically significant. IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

Study subjects

All 57 patients screened for this study were consented, stratified and randomised to an intervention group (Fig. 2). Of these, 31

subjects underwent craniostomosis surgery and 26 subjects underwent scoliosis surgery. The two intervention groups within both stratified procedures had similar characteristics and no differences in baseline laboratory data, except for a slightly higher FIBTEM MCF in the early substitution group of the scoliosis surgery stratum (Table 1).

As a result of unexpected changes in the surgical faculty and subsequent difficulties in recruitment, the study was terminated in October 2014 after 57 (instead of 60) subjects were randomised. A total of 7 subjects in the scoliosis surgery group did not meet criteria for substitution of fibrinogen and were excluded from the final analysis. As a result of an unexpected change in the surgical procedure, one child in the craniostomosis group was excluded after randomisation, as the procedure and the expected blood loss were considered not comparable by the surgeon.

Primary and secondary endpoints

The intention-to-treat analysis of all subjects revealed a reduction in transfusion of RBCs in the early substitution group, 21 ml kg⁻¹ (IQR; 13 to 31 ml kg⁻¹), compared with the conventional group, 28 ml kg⁻¹ (IQR; 18 to 57 ml kg⁻¹) ($P = 0.13$). To adjust for this confounder, multiple linear regression was performed and demonstrated that the type of surgery ($P < 0.001$) and maintenance of normal fibrinogen concentrations ($P = 0.02$), were independent predictors of volume of transfused RBCs kg⁻¹ body weight (adjusted R-squared 0.57).

In the craniostomosis surgery group, subjects treated with fibrinogen concentrate, using a trigger of FIBTEM MCF <13 mm (early substitution group), received significantly less RBCs during the 24 h after the start of surgery (median, 28 ml kg⁻¹; IQR, 21 to 50 ml kg⁻¹), compared with the trigger for fibrinogen substitution of FIBTEM MCF <8 mm (conventional group; median, 56 ml kg⁻¹; IQR, 28 to 62 ml kg⁻¹) ($P = 0.03$). A median of 2 RBC Units (IQR, 1–2 Units) was used in the conventional group (2 donor exposures), and a median of 1 RBC unit (IQR, 1–2 units) were used in the early substitution group (1 donor exposure) ($P = 0.13$). Autologous blood transfusion (MAT) was not used in this study group, as no child fulfilled departmental criteria of body weight >10 kg.

Calculated total blood loss based on blood volume was significantly higher in the conventional group (median 160%; IQR, 110–190%) as compared with the early substitution group (median 90%; IQR, 78–110%) ($P = 0.02$).

In scoliosis surgery, no significant differences for transfused RBCs and MAT were observed between groups (Fig. 3): 6 out of 10 subjects (60%) had no intra or postoperative blood transfusion in the early substitution group (median 0 ml kg⁻¹; IQR, 0–15 ml kg⁻¹), as compared with 3 out of 9 (33%) in the conventional group using a FIBTEM MCF <8 mm (median, 18 ml kg⁻¹; IQR, 0–24 ml kg⁻¹; $P = 0.21$). The proportion of MAT to transfused blood transfusion RBC volume was small in all children with no significant difference between intervention groups (median 0 ml kg⁻¹ (IQR, 0–5 ml kg⁻¹) vs. median 0 ml kg⁻¹ (IQR, 0–4 ml kg⁻¹)) ($P = 0.91$).

No postoperative transfusion of RBCs occurred in either group. Platelet transfusion was needed in 2 craniostomosis surgery subjects intraoperatively, and in one subject in the PICU in the conventional group, and for one subject intraoperatively in the early substitution group. Transfusion of FFP occurred once in both groups in the PICU because of prolonged prothrombin time, although no clinically relevant bleeding or blood loss through the drainage tube was noted. For the scoliosis surgery group, no transfusion of either platelets or FFP was necessary.

The average frequency of administering fibrinogen concentrate during surgery was 3 times in both intervention groups for

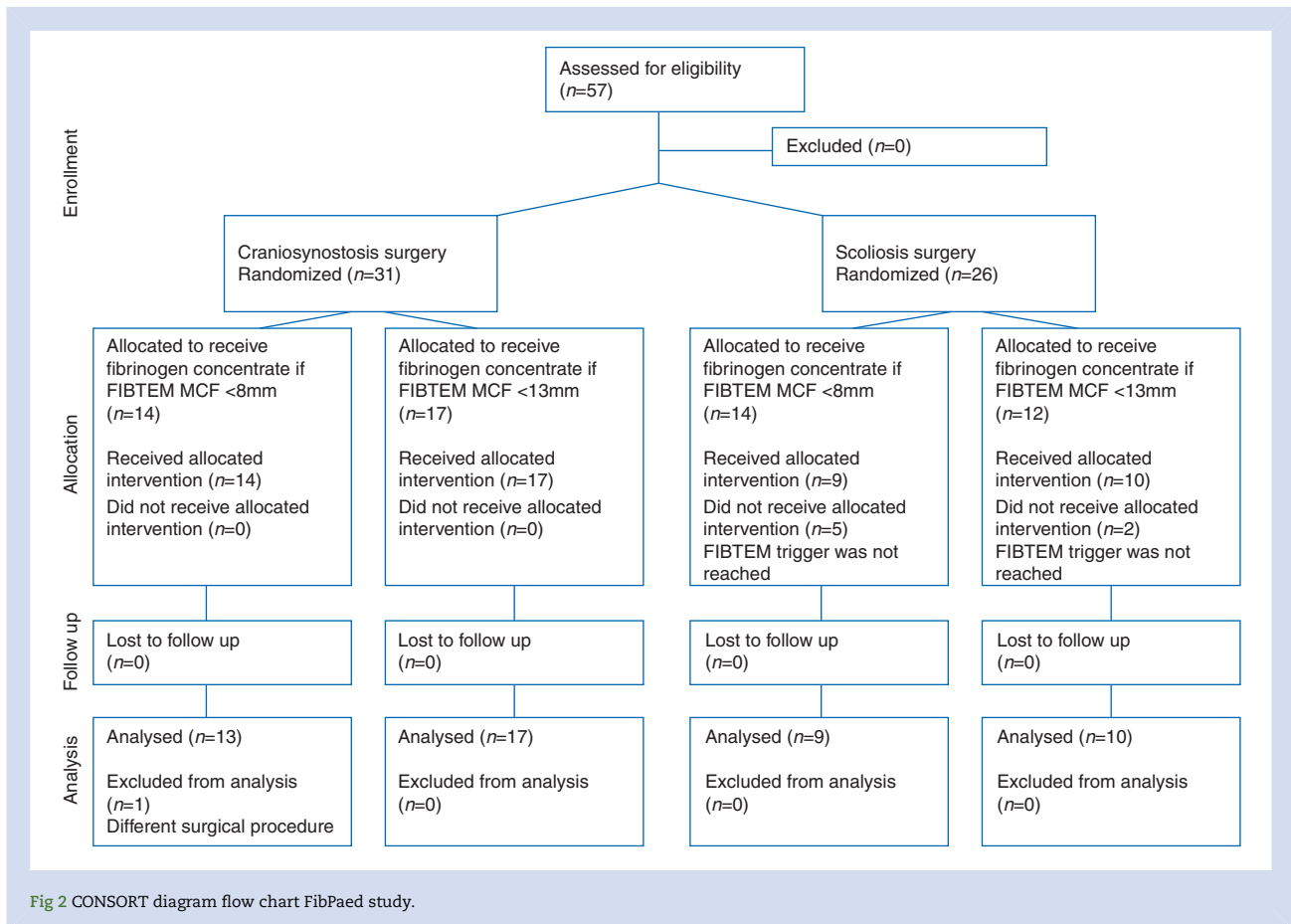


Fig 2 CONSORT diagram flow chart FibPaed study.

craniosynostosis surgery (range 1 to 5). The total dose of administered fibrinogen concentrate per subject was a median of 90 mg kg⁻¹ (IQR, 60–90 mg kg⁻¹) in the conventional group and 90 mg kg⁻¹ (75–120 mg kg⁻¹) in the early substitution group ($P=0.08$).

For scoliosis surgery, fibrinogen was administered an average of 2 times in the early substitution group (range 1 to 3) and one-time in the conventional group (range from 1 to 2). The relative total dose of administered fibrinogen concentrate per subject was a median of 30 mg kg⁻¹ (IQR, 30–60 mg kg⁻¹) in the conventional group and 60 mg kg⁻¹ (30–68 mg kg⁻¹) in the early substitution group ($P=0.28$).

Factor XIII concentrate was administered in 69% (9/13) of subjects in the conventional group and 59% (10/17) of the early substitution group during craniosynostosis surgery, because of low factor XIII concentrations and increased bleeding. During scoliosis surgery, factor XIII was only needed in 11% (1/9) and 20% (2/10) of subjects, respectively (not statistically significant; Table 2). Surgical revision or re-bleeding that required post-operative transfusion during the 24 h after the start of surgery did not occur. There were no between-group differences in length of stay in the PICU or discharge status at 14 days for both surgical procedures (Table 2).

No difference in intraoperative fluid administration was observed in the craniosynostosis surgery group, whereas significantly less crystalloid and colloid were administered in the early substitution group of the scoliosis surgery group (Table 1).

Although the study was not powered to detect differences in safety, no treatment-related adverse events were observed.

Serious adverse events (SAE) were observed in three subjects who underwent scoliosis surgery; none were determined to be treatment related. All subjects fully recovered after a prolonged hospital stay.

Discussion

Early intraoperative fibrinogen substitution, using a trigger level of ROTEM® FIBTEM MCF <13 mm during craniosynostosis surgery, can lead to a significant and clinically relevant reduction in the volume of transfused RBC concentrates, as compared with a conventional trigger level of FIBTEM MCF <8 mm. Furthermore, calculated blood loss decreased from a median of 160% of estimated total blood volume to 90%. In the scoliosis surgery group, the median amount of transfused RBCs decreased from 18 ml kg⁻¹ to no transfusion, but this change was not statistically significant.

To our knowledge this is the first prospective, randomised controlled study demonstrating the successful use of a ROTEM®-guided administration of fibrinogen concentrate during non-cardiac major paediatric surgery. We demonstrated the novel finding that a higher threshold for fibrinogen substitution can reduce blood transfusion in major craniosynostosis surgery. Blood loss during major craniosynostosis surgery has been reported to vary considerably based on the numbers of sutures involved, the length of surgical time, the age at time of surgery, and the presence of craniofacial syndromes.¹⁶ Notably, the observed blood loss in our early intervention group (median 90%) is markedly below the data of the aforementioned study, which reports a

Table 1 Subject characteristics and perioperative data. Data are reported as median (IQR) or n (%) as appropriate. Table includes only subjects treated per protocol. FIBTEM, ROTEM® test assessing fibrinogen polymerisation; A10, amplitude after 10 min; MCF, maximum clot firmness; aPTT, activated partial thromboplastin time; INR, international normalized ratio, Hb, haemoglobin concentration. *Significant difference between treatment groups (Mann-Whitney U-test)

	Trigger to initiate fibrinogen substitution: FIBTEM MCF <8 mm	Trigger to initiate (conventional group) fibrinogen substitution: FIBTEM MCF <13 mm (early substitution group)	P Value
Craniosynostosis surgery (n=30)			
Females	5 (39)	5 (29)	–
Males	8 (61)	12 (71)	–
Age (months)	10 (8–12)	10 (8–11)	0.68
Weight (kg)	9.7 (8.6–10.4)	9.1 (8.3–10.6)	0.59
Height (cm)	74 (70–80)	76 (74–79)	0.30
Preoperative data			
FIBTEM A10 (mm)	9 (9–12)	10 (7–15)	0.46
FIBTEM MCF (mm)	10 (9–13)	10 (8–17)	0.54
FXIII concentration (%)	78 (61–92)	76 (67–97)	0.95
aPTT (s)	31 (30–34)	31 (30–40)	0.48
INR	1.1 (1.0–1.1)	0.9 (0.9–1.1)	0.48
Plasma fibrinogen concentration (mg dl ⁻¹)	180 (159–205)	180 (163–223)	0.68
Platelet count (×10 ⁹ L ⁻¹)	277 (241–321)	281 (230–324)	0.91
Hb (g dl ⁻¹)	10.1 (9.7–11.2)	10.0 (9.4–10.6)	0.51
Leukocytes (×10 ⁶ L ⁻¹)	6.7 (5.7–7.6)	6.8 (5.9–9.6)	0.59
Intraoperative data			
Total volume of crystalloids (ml kg ⁻¹)	68 (49–94)	61 (51–105)	0.90
Total volume of colloids (ml kg ⁻¹)	50 (32–87)	39 (20–63)	0.16
Postoperative data			
Hb 24 h after start of surgery (g dl ⁻¹)	8.7 (7.6–10.3)	7.3 (6.7–9.3)	0.07
Operation data			
Operation time (min)	180 (164–214)	165 (150–174)	0.09
Scoliosis surgery (n=19)			
Females	6 (67)	3 (30)	–
Males	3 (33)	7 (70)	–
Age (yr)	12 (9–13)	12 (10–13)	0.84
Weight (kg)	23.9 (16.8–31.1)	31.6 (26.3–35.7)	0.08
Height (cm)	127 (120–135)	141 (128–150)	0.08
Preoperative data			
FIBTEM A10 (mm)	8 (7–10)	10 (8–12)	0.05
FIBTEM MCF (mm)	9 (7–11)	11 (9–13)	0.03*
FXIII concentration (%)	64 (49–70)	68 (61–88)	0.18
aPTT (s)	32 (30–34)	34 (30–35)	0.50
INR	1.1 (1.0–1.1)	1.0 (1.0–1.1)	0.24
Plasma fibrinogen concentration (mg dl ⁻¹)	190 (145–200)	200 (190–224)	0.10
Platelet count (×10 ⁹ L ⁻¹)	235 (192–257)	246 (184–298)	0.72
Hb (g dl ⁻¹)	11.5 (10.8–12.0)	12.3 (10.5–12.6)	0.28
Leukocytes (×10 ⁶ L ⁻¹)	5.6 (4.2–6.4)	4.2 (3.5–4.9)	0.07
Intraoperative data			
Total volume of crystalloids (ml kg ⁻¹)	73 (47–97)	42 (29–58)	0.01*
Total volume of colloids (ml kg ⁻¹)	28 (17–38)	11 (0–24)	0.04*
Postoperative data			
Hb 24 h after start of surgery (g dl ⁻¹)	8.9 (7.9–10.9)	9.9 (8.7–10.6)	0.66
Operation data			
Operation time (min)	182 (161–242)	168 (145–239)	0.55

blood loss of 148% of estimated total blood volume for multiple sutures, and 110% if mono suture or bicoronal synostosis surgery was performed. To further emphasize the effectiveness of the applied management investigated in this study, no postoperative RBC transfusion in any child was necessary. This is in contrast to published data for children who underwent major craniofacial surgeries, where postoperative transfusion occurred relatively

frequently (26 to 40%).^{17–19} A recent review article concluded that fibrinogen therapy appears to reduce transfusion requirements, but data from further high quality studies are urgently needed to confirm this conclusion.²⁰ Coagulation factor based treatment algorithms have been successfully implemented in various clinical settings and may offer a much faster and more targeted approach to treating coagulopathy.^{11 21–25}

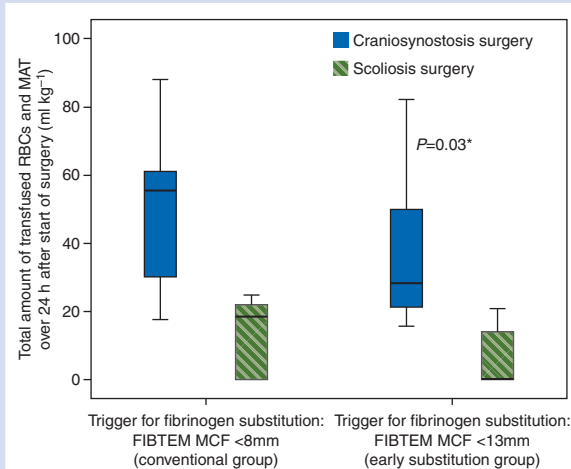


Fig 3 Total amount of transfused RBCs and MAT over 24 h after start of surgery. FIBTEM®, functional fibrinogen assay of ROTEM®; MCF, maximum clot firmness; RBCs, red blood cell concentrate; MAT, mechanically processed autologous transfusion.

The favourable outcome could be attributable to the formation of a more stable clot, and in consequence, to the mitigation of severe coagulopathic bleeding. The importance of fibrinogen and its critical role in the formation of a stable clot and prevention of major perioperative bleeding has been increasingly described.^{26–28} Results from a retrospective data analysis demonstrated that hypofibrinogenaemia is the main underlying reason for intraoperative coagulopathy during craniostomy surgery, and that administration of fibrinogen concentrate can successfully treat acquired bleeding.¹² A similar finding was observed in a retrospective analysis of a larger cohort of children, who underwent the same surgical procedure, demonstrating reduced transfusion requirements if a ROTEM® based treatment algorithm was applied.⁷ In this study, fibrinogen concentrate and factor XIII concentrate were exclusively used to treat intraoperative coagulopathy, whereby the trigger for fibrinogen substitution was set at FIBTEM MCF <8 mm. The current European guidelines for intraoperative bleeding management suggest trigger levels for initiating fibrinogen substitution at plasma fibrinogen concentrations of 150–200 mg dl⁻¹ or ROTEM® FIBTEM MCF ≤7 mm, but evidence based data in children are sparse. The targeted fibrinogen concentration in our early substitution group is about 50% higher than the threshold given in the previously mentioned European guideline.¹¹ However, the higher trigger

Table 2 Study efficacy endpoints. Data are reported as median (IQR) or number (%) as appropriate. Table includes only patients treated per protocol. RBCs, red blood cell concentrates; MAT, mechanically processed autologous transfusion; FFP, fresh frozen plasma; PICU, paediatric intensive care unit. *Significant difference between treatment groups (Mann-Whitney U-test or Fisher's exact test)

	Trigger to initiate fibrinogen substitution: FIBTEM MCF <8 mm (conventional group)	Trigger to initiate fibrinogen substitution: FIBTEM MCF <13 mm (early substitution group)	P Value
Craniosynostosis surgery			
Primary endpoint			
Total amount of transfused RBCs over 24 h after start of surgery (ml kg ⁻¹)	55.5 (27.5–61.8)	28.2 (21.2–49.9)	0.03*
Secondary endpoints			
Total amount of transfused platelet concentrate over 24 h after start of surgery (ml kg ⁻¹)	0 (0–5)	0 (0–0)	0.43
Total amount of transfused FFP over 24 h after start of surgery (ml kg ⁻¹)	0 (0–0)	0 (0–0)	0.97
Administration of FXIII concentrate (%)	9 (69)	10 (59)	0.41
Calculated total blood loss (%)	156.9 (110.5–187.3)	89.7 (77.7–112.9)	0.02*
Length of stay in PICU (days)	1 (1–1)	1 (1–1)	0.59
Length of stay in hospital (days)	9 (9–9)	9 (9–9)	0.54
Surgical revision because of bleeding (%)	0	0	1.0
Scoliosis surgery			
Primary endpoint			
Total amount of transfused RBCs and MAT over 24 h after start of surgery (ml kg ⁻¹)	18.4 (0–23.8)	0 (0–15.3)	0.21
Secondary endpoints			
Total amount of transfused MAT (ml kg ⁻¹)	0 (0–5.2)	0 (0–4.1)	0.91
Total amount of transfused platelet concentrate over 24 h after start of surgery (ml kg ⁻¹)	0 (0–0)	0 (0–0)	1.0
Total amount of transfused FFP over 24 h after start of surgery (ml kg ⁻¹)	0 (0–0)	0 (0–0)	1.0
Administration of FXIII concentrate (%)	1 (11)	2 (20)	0.54
Calculated total blood loss (%)	51.0 (38.5–69.2)	36.5 (14.9–54.3)	0.17
Length of stay in PICU (days)	1 (1–1)	1 (1–1)	0.50
Length of stay in hospital (days)	8 (6–13)	8 (8–10)	0.57
Surgical revision because of bleeding (%)	0	0	1.0

was intentionally selected with the aim of avoiding the occurrence of hypofibrinogenaemia-induced coagulopathy, which usually develops rapidly during these procedures. In addition, the resulting fibrinogen concentrations were still within the normal range of published reference ranges for ROTEM® in children,²⁹ and thus unlikely to lead to adverse effects from overdosing.

Additional factors that were likely to reduce the bleeding tendency in our patient population include prophylactic use of antifibrinolytics (TXA) and additional monitoring and substitution of factor XIII concentrations. The clinical benefit of prophylactic TXA administration to significantly decrease perioperative bleeding and blood transfusion requirements has been confirmed for both craniosynostosis and scoliosis paediatric surgery.^{18 30 31} In contrast, the occurrence of low factor XIII concentrations appears to be frequently present during major paediatric surgery,¹³ but data to support routine substitution for treatment of acute bleeding are not available. However, there is no doubt that factor XIII is required to form a stable clot.³² As the applied coagulation management in this study did not include the routine use of products that provide a source of FXIII, such as fresh frozen plasma or cryoprecipitate, we implemented the additional targeted factor XIII substitution in our local transfusion algorithm.

Effective coagulation management requires a combination of applied treatment options, surgeon experience and technique, and the ready availability of diagnostic testing. In this study, use of ROTEM® thromboelastometry was a main pillar in the timely measurement and targeted administration of coagulation factors. In severely bleeding infants, changes in haemostatic profile develop within minutes, making it impossible to wait for the results of standard coagulation testing, such as fibrinogen concentration in order to determine hypofibrinogenaemia. The clinical use of point-of-care testing has markedly improved this unacceptable time delay and ROTEM®-guided transfusion algorithms have demonstrated a reduction in the amount of perioperative blood transfusion.^{11 33–35} The FIBTEM test is designed to evaluate clot firmness while platelet contribution is chemically blocked; thus the amplitude reflects the fibrin polymerization process, which is completely different from the method used in the standard Clauss fibrinogen assay.³⁶ Recent literature has demonstrated that the amplitude of the FIBTEM test can be safely assessed and used for diagnostic decisions after only 5 min (A5 value), which would further expedite coagulation management.^{37 38}

Notably, no difference was observed in terms of the total dose of fibrinogen administered between both treatment groups in either type of surgery. One could speculate that this demonstrates the very effective result of the continuous ROTEM®-guided fibrinogen administration, simply using a higher trigger level and earlier initiation in the early substitution group.

No SAE related to study treatment was observed in any subject, which is in accordance with published data that indicate that fibrinogen concentrate offers a good safety profile and should not place patients at additional risk for thromboembolic side effects.^{8 39}

Limitations to the study

The study was designed as a single centre study with a small sample size per group. As a result of unexpected problems with scheduled eligible patients, the study was terminated after it had been prolonged for 9 months (amendment to the study protocol), which affected the primary power analysis. The

unexpectedly large number of subjects who did not receive any RBC transfusions further weakened the initial power calculation. However, statistical analyses have confirmed the assumption that using a higher fibrinogen concentration to initiate fibrinogen substitution was linked to a nearly 50% decrease in transfused RBCs during the 24 h after the start of surgery, which was the primary endpoint. Another limitation is that the sample size was too small to provide robust data regarding safety problems and the study was not powered to evaluate safety. The trigger level of <13 mm FIBTEM MCF in the early substitution group was determined based on our own observations that were performed previously in this patient population. However, in this study, baseline FIBTEM MCF tended to be lower than median levels of our previous study, which resulted in earlier substitution of fibrinogen in the early substitution group. Finally, intraoperative staff and study team members were not blinded to the randomization. To mitigate this limitation, we used a strictly-enforced transfusion algorithm and blinded postoperative caregivers.

Conclusions

This study demonstrated that a higher trigger level for fibrinogen administration, using a ROTEM® FIBTEM MCF trigger level of <13 mm, can decrease bleeding and the transfusion of RBCs in the setting of craniofacial surgery. This regimen may be considered and further investigated as an alternative approach to decrease paediatric perioperative bleeding in clinical scenarios other than craniosynostosis surgery, thereby reducing exposure to allogeneic blood products.

Authors' contributions

T.H. was the principal investigator and contributed to the study design, data analysis and writing of the paper. N.S. contributed to the study design and data collection. T.R. contributed to the study design and manuscript writing. B.S. contributed to data analysis and manuscript writing. G.H. contributed to data collection and manuscript writing. All of the authors read and approved the final manuscript.

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